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EXAMINER	
EPPS FORD, JANET L	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 11/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/817,387	MATTHES ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. *09/423,157* .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Response to Amendment

1. The amendment to the claims filed on 8-22-03 does not comply with the requirements of 37 CFR 1.121(c) because Applicant's have deleted the terms "n> 10; $\leq$ 20" and "n_1 > 3; $\leq$ 17," and have added the limitations "n is at least 10 and not more than 20," and "n_1 is at least 3 and not more than 17." However, there are no markings indicating that these changes have been made. Amendments to the claims filed on or after July 30, 2003 must comply with 37 CFR 1.121(c) (2) which states:

"(2) *When claim text with markings is required.* All claims being currently amended in an amendment paper shall be presented in the claim listing, indicate a status of "currently amended," and be submitted with markings to indicate the changes that have been made relative to the immediate prior version of the claims. **The text of any added subject matter must be shown by underlining the added text. The text of any deleted matter must be shown by strike-through except that double brackets placed before and after the deleted characters may be used to show deletion of five or fewer consecutive characters.** The text of any deleted subject matter must be shown by being placed within double brackets if strike-through cannot be easily perceived. Only claims having the status of "currently amended," or "withdrawn" if also being amended, shall include markings. If a withdrawn claim is currently amended, its status in the claim listing may be identified as "withdrawn—currently amended."

Election/Restrictions

2. In the Amendment filed 4-01-03 Applicants provisionally elected with traverse, Group I, drawn to chimeric oligonucleotides having a phosphorous containing backbone, instead of the chimeric oligonucleotides comprising a polyamide backbone as set forth in Group II. Additionally, Applicant's provisionally elected with traverse the chimeric oligonucleotide described in SEQ ID NO: 16. Applicants traversed the basis for the Election/Restriction requirement on the grounds that the examiner allegedly applied the wrong legal standard. Applicants argued that a Lack of Unity of Invention should have been applied since the instant

application is a national stage application of a PCT application. However, contrary to Applicant's assertions, the instant application is a continuation in part of national stage application 09/423,157. According to MPEP § 1895.01 [R-1] "[A] continuing application claiming benefit under 35 U.S.C. 365(c) to an international application or to a national stage application is not a national stage application and, therefore, the restriction practice under 35 U.S.C. 121 is applicable."

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, and those claims dependent therefrom, claims 2-11, recites the limitations "the RNA component" and "the telomerase," however there is a lack of antecedent basis for these limitations in claim 1.

The structure of general Formula I recited in claim 1 is vague and indefinite. Specifically, the relationship between the repeating units []n and []n_1 of the R group is unclear. For example, it is unclear if the R group in general formula I is to be substituted with a repeating unit of n1 wherein n1 is at least 3 and not more than 17, and further wherein the repeating unit n1 of R is substituted into general formula I and further repeated at least 10 times and not more than 20 times.

Moreover, the phrase "capable of hybridizing to the RNA component of the telomerase," is vague and indefinite since the metes and bounds of the term "hybridizing" as used in this context is unclear. For instance it is not clear under what conditions hybridization is occurring, if it is not specific hybridization under low stringency conditions or specific hybridization under highly stringent conditions. The conditions of hybridization would also provide some guidance as to the nucleotide structure of the oligonucleotide. However, in the instant case it is unclear which telomerase Applicants are referring to, since the claim recites "the telomerase," and there is no sequence information recited such that one of skill in the art would be able to determine the structures of oligonucleotides that would "hybridize" to said telomerase, assuming that the claim is referring to a nucleotide sequence.

Claims 9-10, recite the limitation "said binding to telomerase," however there is insufficient antecedent basis for this limitation in the claims.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 7-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using chimeric oligonucleotides according to the present invention to inhibit telomerase activity *in vitro* comprising the administration of chimeric oligonucleotides of SEQ ID NO: 1-29, does not reasonably provide enablement for using chimeric oligonucleotides of undefined structure and/or target, *in vivo* for treatment purposes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

The specification as filed is directed to the use of chimeric oligonucleotides comprising a sequence that is complementary to the TTAGGG telomerase RNA hexanucleotide. There is no direction for the inhibition of telomerase activity using chimeric oligonucleotides of undefined nucleic acid composition. Claims 7-8 clearly encompass the use of chimeric oligonucleotides of undefined nucleobase composition. Furthermore, claim 8 clearly encompasses a broad method for treatment of tumours comprising administration of a chimeric oligonucleotide of undefined nucleobase composition.

In regards to the therapeutic use of oligonucleotides *in vivo,* the state of the art indicates that delivery of these oligonucleotide compositions for therapeutic purposes "remains an important and inordinately difficult challenge (Chirila et al., 2002; see abstract)." Chirila et al. page 327, last paragraph) teach that "[T]he in vivo delivery techniques chiefly used at the present, i.e. infusion or injection of naked molecules and liposomal systems, do not assure adequately long-term maintenance of ODNs (oligonucleotides) in tissues," which is required to achieve therapeutic effects. As a conclusion to the review of Chirila et al., the state of oligonucleotide based drug therapy is summarized by the statement: "the antisense strategy only awaits a suitable delivery system in order to live up to its promise." Therefore, the efficacy of antisense based therapies hinges upon the ability to deliver a sufficient amount of oligonucleotide, to the appropriate tissues, and for a sufficient period of time, to produce the desired therapeutic effect. So far, it appears that all of the developments in antisense based therapies have not been sufficient to overcome this one basic obstacle, drug delivery. Furthermore, Applicant's specification does not provide actual working examples or guidance so that the skilled artisan can deliver the pharmaceutical compositions of the claimed invention to

target tissues successfully, to produce the desired therapeutic result without undue experimentation.

Jen et al. (*Stem Cells,* Vol. 18: 307-319, 2000) provide a review of the challenges that remain before antisense-based therapy becomes routine in therapeutic settings. According to Jen et al. many advances have been made in the antisense art, but also indicate that more progress needs to be made. Moreover Jen et al. conclude that "[g]iven the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has remained elusive." It is also concluded that "[a] large number of diverse and talented groups are working on this problem, and we can all hope that their efforts will help lead to establishment of this promising form of therapy." (See page 315, last two paragraphs).

Additionally, according to Stein (2000) "[A]ntisense oligonucleotide biotechnology has entered a phase of its development in which many problems engendered by non-sequence specificity are being recognized and being actively addressed. However, in order to improve specificity of the methodology, attention must now also be paid to co-suppression of gene activity due to irrelevant cleavage." Stein further states that "[T]o the extent that this issue also is addressed, correlations between the down-regulation of a defined target and an observed biological outcome (e.g., growth suppression) eventually *[emphasis added]* may be possible." (page 235, Concluding remarks) Stein clearly suggests that use of antisense oligonucleotide therapeutics are highly unpredictable due to "irrelevant cleavage" as a result of the low stringency requirements for RNAse H activity, wherein a 5-base complementary region of oligomer to target may be sufficient to elicit RNAse H activity (see Stein, abstract).

Moreover, Chirila et al. (2002), Jen et al. (2000), and Stein (2000) teach that the behavior of oligonucleotide based compositions and their delivery *in vivo* are unpredictable, therefore claims to pharmaceutical compositions and methods of treating diseases by the administration of oligonucleotide based pharmaceuticals are subject to the question of enablement due to the high level of unpredictability associated with this technique as taught in the prior art.

The quantity of experimentation required to practice the invention as claimed would require determining modes of delivery in a whole organism such that an undefined target nucleic acid is inhibited and the desired secondary effect of treating tumors is obtained. The specification as filed provides no specific guidelines in this regard; the specification merely provides a prophetic example for using the claimed compositions *in vivo*. The deficiencies in the specification would constitute undue experimentation since these steps must be achieved without instruction from the specification before one is enabled to practice the claimed invention.

Therefore, the specification as filed does not teach the skilled artisan how to use the chimeric oligonucleotides of undefined nucleobase composition, according to the present invention for inhibiting telomerase activity *in vitro* or *in vivo* treatment purposes, without undue experimentation. This conclusion is based upon the known unpredictability regarding the behaviour of oligonucleotide compositions in a cell, delivery of antisense *in vivo,* irrelevant cleavage of non-specific targets, the quantity of experimentation required to practice the full scope of the claimed invention (which reads on the therapeutic use of the claimed pharmaceutical composition) and the lack of guidance thereof in the specification as filed in this regard.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Ulhmann et al.

Due to the uncertainty in regards to the structure of the compounds according to general formula I recited in the instant claims, and further with the uncertainty associated with the nucleotide structure of the chimeric oligonucleotides according to the present invention, the prior art is applied to the extent that the prior art compounds have an over all length of at least 10 and no greater than 20 nucleotides in length (i.e. the definition of n, not n1).

Uhlmann et al. disclose compounds according to the present invention, wherein said compounds comprise a 5' DNA portion and a 3' PNA portion or 3' DNA portion. For example, see Tablelle 1, sequenz 6, or sequenz 14. The compounds of Ulhmann et al. are at least 10 nucleotides in length and no greater than 20 nucleotides in length. See also structure 1a on page 2794, Figure 1, which shows the structure of the DNA-PNA compounds of Uhlmann et al., note that there is a 5'-OH group at the 5' most portion of the molecule.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 703-308-8883. The examiner can normally be reached on Monday-Thursday, 8:30 AM - 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Janet L. Epps-Ford, Ph.D.
Examiner
Art Unit 1635

JLE